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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/152,698	09/02/1998	REGUPATHY MADIYALAKAN	AREX-P02-004	4505

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/152,698	MADIYALAKAN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 30,71,75,76,85-89,93,95,96 and 98-122 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 30,71,75,76,85-87,89,93,95,96 and 98-122 is/are rejected.

7)☐ Claim(s) 88 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 30, 71, 85, 86, 104110 have been amended. Claims 116-122 have been added. Claims 30, 71, 75, 76, 85-89, 93. 95, 96 and 98-122 are pending and under consideration.

Text of Title 35, U.S. Code, not found in this action can be found in a previous action.

Claims 103-106, 108, 109, 119 and 122 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a method wherein cytotoxic T-cells are induced which are reactive with at least one other epitope of the tumor associated antigen. The specification describes a method wherein the administration of an antibody-tumor antigen complex induces antibodies which are reactive with at least one other epitope associated with the tumor associated antigen (Example 1) and the concurrent activation of cytotoxic T-cells in the case of CA125 (Example 2). The specification does not provide support for the broad method wherein said T-cells are cytotoxic T-cells, or wherein said T-cells are reactive with at least one other epitope within the tumor associated antigen.

Claims 30, 71, 75, 76, 85, 86, 87, 89, 93, 95-122 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an oncological disease comprising administering to a host a complex formed from CA125 and a monoclonal antibody or antigen-binding fragment thereof that binds to CA125, and wherein the complex induces host antibodies and cytotoxic T-cells reactive with at least one other epitope of the tumor associated antigen, does not reasonably provide enablement for the administration of any other complex of a soluble tumor antigen and a monoclonal antibody or antigen-binding fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized by In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claim require the treatment of any oncological disease comprising the stimulation of a multi-epitopic immune response carried out by the administration of the soluble antigen of the oncological disease and a monoclonal antibody that binds thereto. The immune response encompassed by the claims includes both the tumor immune response and a cellular immune response which includes the generation of cytotoxic T lymphocytes. The specification and art of record indicates that administration of the Mab 43.13 which bind to circulating tumor antigen in the blood of ovarian cancer patients resulted in the unexpected long survival times of these patients. The specification teaches that the presence of the circulating tumor antigen in the blood complexed with the administered antibody. The specification teaches that the administration of the antigen-antibody complex rather than the antigen alone results in a humor response comprising antibodies which bind to multiple epitopes on the antigen, as well as a T-cell response in conjunction to the humoral response. The art teaches that Th1 cell-mediated immunity is critical for the induction of an anti-tumor response (Nishimura et al, Cancer Chemother Pharmacol, 2000, Vol. 46, suppl. pages S52-S61). The art teaches that cancer patients are often tolerized to their respective tumors (Sotomayor et al, Critical Reviews in Oncogenesis, 1996, Vol. 7, pp. 433-456, provided in the Declaration of Aug 9, 2005). The art

teaches that the presence of the antibody complexed to the antigen changes the recognition of the immunological determinants within the antigen (Simitsek et al, J Exp Med, 1995, Vol. 181, pp. 1957-1963, cited in a prior action; Watts et al, J Exp Med, 1993, Vol. 178, pp. 1495-1463). The art teaches that tolerance to a protein involves tolerance to the immunodominant determinants rather than the subdominant determinants (Cibotti et al PNAS, 1992, Vol. 89, pp. 416-420). It is noted that the abstract of Pani et al (Immunological Investigations, 1994, Vol. 23, pp. 337-346) reports that "tolerance to a self protein shows the same phenomenon seen for non self proteins". The art teaches that disruption of the determinant hierarchy (dominant versus subdominant) can result in the priming of an immune response to a subdominant or cryptic self-determinant (Benichou et al, 1994, Vol. 6, pp. 131-138). However, neither the specification nor the art teaches how to reliably expose subdominant epitopes on soluble tumor antigens that will be effective to treat an oncological disease. It is noted that a monoclonal antibody would bind only to a single epitope on a tumor antigen. According to the art this would suppress the recognition of that epitope when taken up by an antigen presenting cell due to the physical binding of said antibody, and the persistence thereof within said cell. In order for the treatment to be effective, immune recognition of a subdominant epitope of the tumor antigen must effectively generate cytotoxic T-cells that recognize and cell of the oncological disease. The specification provides no teachings on how to select a subdominant epitope(s) for enhancement by the suppression of the immunodominant epitope in an antibody-antigen complex. It is noted that the administration of the antigen antibody complex can result in the priming of the immune response to subdominant epitopes of the soluble tumor antigen which are not accessible on the tumor surface by virtue of the conformation of said tumor antigen while part of the tumor surface.

The art teaches that the generation a quantifiable CTL in the peripheral blood of cancer patients, such a CTL response, is not associated with clinical evidence of tumor regression (Lee et al, Journal of Immunology, 1999, Vol. 163, pp. 6292-6300). Further, Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject

tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). Thus, there appears to be no nexus between the presence of CTL in vivo and an anti-tumor response in an individual, and further, there is not teachings for the selection of a subdominant epitope wherein priming to said subdominant epitope can result in a CTL which recognizes tumor antigen on the tumor cell surface.

The prior art teaches that tumor cells are phenotypic ally less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4).

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al, International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed complex upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teach that the failure of methods of treating cancer comprising the administration of compositions which are designed to render an immune response against the tumor based on recognition of the tumor antigen is due to the failure to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Due to the unreliability of the art as discussed above, the lack of a working example which demonstrates the successful treatment of a subject with an antigen antibody complex beyond that of Mab 43.13 bound to soluble CA125, one of skill in the art would be subject to

undue experimentation without reasonable expectation of success in order to practice the broadly claimed method.

Claim 88 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth or maintained in the prior Office action are withdrawn in light of applicant's arguments and amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/31/2005